Remarks

Claims 1-10, 12, 14-18, 20-26, 28 and 30-41 are pending in the present application. Claim 27 has been cancelled. The following objections and rejections are at issue and are set forth by number in the order in which they are addressed:

1. Claim 27 is objected to as being an improper dependent claim;
2. The claims are rejected for double patenting;
3. Claims 1-10, 12, 14-18, 20-28 and 30-41 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing new matter;
4. Claims 1-10, 12, 14-18, 20-28 and 30-41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor in views of Felts and Inaba et al.;
5. Claims 1-10, 12, 14-18, 20-28 and 30-41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor in views of Felts and Inaba et al., in further view of Burns et al.;
6. Claims 1-10, 12, 14-18, 20-28 and 30-41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor in views of Felts and Inaba et al., in further view of Schroder et al.;
7. Claims 1-10, 12, 14-18, 20-28 and 30-41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor in views of Felts and Inaba et al., in further view of Primus and Kolb et al.;
8. Claims 1-10, 12, 14-18, 20-28 and 30-41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor in views of Felts and Inaba et al., in further view of Naldini et al.

Claim 28 has been amended in order to further Applicant's business interests and the prosecution of the present application in a manner consistent with the PTO's Patent Business Goals (PBG; 65 Fed. Reg. 54603 (September 8, 2000), and not in acquiescence to the Examiner's arguments and while reserving the right to prosecute the original (or similar) claims in the future. None of the claim amendments made herein are intended to narrow the scope of any of the

amended claims within the meaning of *Festo Corp. v. Shokestu Kinzoku Kogyo Kabushiki Co.*, 234 F.3d 558, 56 USPQ2d 1865 (Fed. Cir. 2000) or related cases.

1. The objection to Claim 27 is moot

Claim 27 has been cancelled and thus the objection to Claim 27 as being an improper dependent claim is moot.

2. Double patenting.

A terminal disclaimer will be filed upon resolution of the remaining rejections.

3. The claims do not contain new matter.

Claims 1-10, 12, 14-18, 20-28 and 30-41 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing new matter. Applicants again stress that the claimed range of 20 to 100 integrated vectors is clearly within the described range of 5 to 100 integrated vectors per cells. The subject matter of claim need not be described literally or "in ipsis verbis" in order for the specification to satisfy the written description requirement. See, e.g., In re Lukach, 442 F.2d 967, 969, 169 USPQ 795, 796 (C.C.P.A. 1971). It is clear that the claimed lower limit of 20 integrations per cell is within the ranges taught in the specification. The Examiner' arguments with respect to Wertheim fail to address the fact that the ranges in the currently pending claims are within the ranges of the original claims and are thus proper.

In any event, parent application 09/897,511, now issued U.S. Pat. No. 6,852,510, which is incorporated by reference, discloses at Column 2, lines 20-35 that:

> The present invention is not limited to host cells transfected with a particular number of integrating vectors. Indeed, host cells containing a wide range of integrating vectors are contemplated. In some embodiments, the present invention provides a host cell comprising a genome containing preferably at least about two integrated integrating vectors. In still further embodiments, the genome preferably comprises at least 3 integrated integrating vectors and most preferably at least 4 integrated integrating vectors, 5 integrated integrating vectors, 6 integrated integrating vectors, 7 integrated integrating vectors, 10 integrated integrating vectors, 15 integrated integrating vectors, 20

integrated integrating vectors, or 50 integrated integrating vectors.

As such, the claim limitation of 20 to 100 integrated vectors per cell is specifically supported by reference. Applicants respectfully request that this ground of rejection be withdrawn.

4. The claims are not obvious over Mathor, Felts and Inaba.

Claims 1-10, 12, 14-18, 20-28 and 30-41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor in views of Felts and Inaba et al. Applicants respectfully traverse.

Applicants respectfully submit that the Examiner's reasoning with respect to the teachings of Mathor, Felts and Inaba are inconsistent with the understanding of one of skill in the art when considering the art as a whole. The Examiner argues that Mathor clearly teaches that sysntheis of exogenous protein is proportional to the number of retroviral vectors and that Felts teaches that that the number of retroviruses integrated can be controlled by controlling MOI. Office Action at 7. The Examiner then argues that based on these teachings, one of skill in the art would have known to increase the production of a desired protein by increasing the number of viral integrations and would have known to increase integrations by increasing MOI.

The Examiner's attention is respectfully directed to the accompanying Declaration of Dr. Gregory Bleck, one of the inventors of the instant application and person of ordinary skill in the art. As stated by Dr. Bleck, the Examiner's reasoning respect to what the art as a whole teaches is wrong:

> The art teaches away from producing cell lines by using a high MOI's, such as an MOI of 100, and also teaches away from the production of cell lines with more than 20 intregrated vectors per cell. Coffin et al., Development and Applications of Retroviral Vectors, Chapter 9 in Retroviruses, 1997, p. 437-473, which was cited by the previous Examiner on Form PTO-829 mailed November 17, 2005, teaches at page 463, column 1 that: "Insertional mutagenesis by retroviral vectors is often cited as a safety concern. This issue has been raised because proviral insertion can cause the inactivation of tumor

suppressor genes or the activation of oncogenes." Furthermore, references such as Arai et al., Virology 260:109-115 (1999), which was cited by the previous Examiner on Form PTO-829 mailed November 17, 2005, specifically teach away from the current claims. Arai et al. state:

> When a 3Y1 was transduced with the pseudotyped vector at an m.o.i. of 100, a significant proportion of the cell population became detached from the plate within two days. Since apoptotic cells were detected from among these cells at 1 day after transduction by means of the TUNEL method (data not shown), proviral integration with a very high copy number seems to cause cell death. While we did not address the reason for this induction of apoptosis, a major factor could be that the multiple integration causes insertional mutagenesis in essential genes. The toxicity of overproduced LacZ was not the major reason, because LacZ activity observed in 3Y1 transduced at m.o.i. 100 at 1 day after the transduction was less than that detected in 3Y1 transduced at m.o.i. 30 at 3 days after the transduction, and the latter cells showed only marginal signs of apoptosis (data not shown).

Thus, Arai teaches that "proviral integration with a very high copy number seems to cause cell death." Upon reading reading Arai, one of skill in the art would be "discouraged" from using a the claimed multiplicity of infection and copy insert number to obtain cells for the production of a secreted protein.

5. The Examiner attempts to distinguish Coffin et al. by arguing that it is noted that Coffin refers to in vivo use of retroviral vectors in human and animals and not to in vitro use as presently claimed. This is not a valid distinction. A person of skill in the art, reading Coffin et al., would be discouraged from using transduction conditions that lead to high numbers of integrations and insertional mutagenesis. Such concerns would apply in vivo or in vitro.

6. The Examiner admits that Arai et al. teaches that proviral integration with a high copy number seems to cause cell death. The Examiner attempts to distinguish Arai et al. by arguing that Arai et al. do not teach what a very high copy number means. A person of skill in the art, reading Arai et al., would understand Arai et al. to teach away

from using conditions that could lead to insertional mutagenesis and cell death. The person of skill in the art understands that conditions that would result in more than 15 integrations fall within this category and thus be discouraged from exceeding the conditions taught by Arai. Thus, one of skill in the art would not have known to use MOIs between 30 and 100 to obtain more than 15 integrations and would not have known to use routine experimentation to determine what MOIs result in 20 to 100 integrations. In fact, a person of skill in the art, reading Arai et al., would have been discouraged from such experiments because Arai teaches that insertional mutagenesis and cell death would result.

7. The Examiner's reliance on Taruscio et al. as teaching the meaning of high copy number is inappropriate. Taruscio et al. addresses the copy number of endogenous retroviruses that have integrated into the genome over millions of years, and perhaps been duplicated by chromosomal rearrangement over that extreme time period. This is a different context than the exposure of cultured cells to concentrated levels of retroviral vectors in vitro. Arai et al. and Coffin et al. address exactly the conditions at issue, i.e., transduction of cells with concentrated retroviral vectors, and conclude that such conditions cause insertional mutagenesis and cell death. One of skill in the art is discouraged from using such conditions. The prior art clearly warns of the risks associated using conditions that lead to greater than 15 integrations per cell.

As indicated by Dr. Bleck, a person of skill in the art considering the art as a whole would be discouraged from producing the claimed cells using the claimed conditions because they would have thought that those conditions would lead to cell death. To a person of skill in the art, the fact that Coffin is directed to use in vivo does not mitigate Coffin's teaching that insertional mutagenesis is a problem that should be addressed and avoided. Indeed, as stated by Dr. Bleck, Arai et al. and Coffin et al. address exactly the conditions at issue, i.e., transduction of cells with concentrated retroviral vectors, and conclude that such conditions cause insertional mutagenesis and cell death. One of skill in the art is discouraged from using such conditions. Thus, the Examiner's arguments are misguided.

Likewise, the Examiner's arguments with respect to Arai et al. and Taruscio and the meaning of very high copy number are not consistent with what one of skill in the art would conclude. As stated by Dr. Bleck, A person of skill in the art, reading Arai et al., would understand Arai et al. to teach away from using conditions that could lead to insertional mutagenesis and cell death. The person of skill in the art understands that conditions that would result in more than 15 integrations fall within this category and thus be discouraged from exceeding the conditions taught by Arai. Thus, one of skill in the art would not have known to use MOIs between 30 and 100 to obtain more than 15 integrations and would not have known to use routine experimentation to determine what MOIs result in 20 to 100 integrations. In fact, a person of skill in the art, reading Arai et al., would have been discouraged from such experiments because Arai teaches that insertional mutagenesis and cell death would result. Furthermore, as indicated by Dr. Bleck., a person of skill in the art would not look to an unrelated reference such as Taruscio for the meaning of very high copy number. This combination amounts to nothing more than hindsight reconstruction.

According to the Supreme Court, obviousness analysis requires: A) Determining the scope and content of the prior art; B) Ascertaining the differences between the prior art and the claims in issue; C) Resolving the level of ordinary skill in the art; and D) Evaluating evidence of secondary consideration of nonobviousness. Graham v Deere, 383 US 1, 17-18 (1966); MPEP 2414I. The Supreme Court recently addressed the issue of obviousness in KSR Int'l Co. v. Teleflex, Inc. 127 S. Ct. 1727 (2007).

The KSR Court reiterated the Graham test for obviousness. The KSR Court recognized that most, if not all, invention "rely upon building blocks long since uncovered, and claimed discoveries most of necessity will be combinations of what, in some sense, is already known." KSR, 127 S. Ct. at 1741. The Court further recognized that the "combination of familiar elements according to known methods is likely to be obvious when it does no more than yield **predictable results**." Id. at 1739. (emphasis added). The Court noted that where the prior art teaches away from a claimed invention, the invention is most likely patentable. To illustrate this principle, the Court relied on its holding in United States v. Adams, 383 U.S. 39, 40 (1966). In Adams, the Court found the invention (a battery) was not obvious because the prior art taught away from combining certain known elements. In particular, the prior art warned that risks were

involved in using the types of electrodes Adams employed. Id.

The KSR Court provided the following guidelines for determining obviousness. Where the invention combines known elements by substituting one element for another element or using a known technique to improve a device, "a court must ask whether the improvement is more than a **predictable use** of prior art elements according to their established functions." *Id*. at 1740. (Emphasis added). This is different from the case "where the claimed subject matter may involve more than simple substitution of one known element for another or the mere application of a known technique to a piece of prior art ready for the improvement." *Id*. at 1740-41. There, in order to determine if there was an apparent reason to combine the known elements in the fashion claimed, it will be necessary to consider:

1) the interrelated teachings of multiple patents;

2) the effects of demands known to the design community or present in the marketplace; and

3) the background knowledge possessed by a person having ordinary skill in the art. Id.

The instant case is subject to the second analysis because the Examiner has previously admitted that the art does not teach the claimed number of integrations. Applicants arguments above address the interrelated teaching of the art, the demands of the community, and the background knowledge possessed by one of skill in the art. The fact is that the art teaches away from the producing cells lines with the claimed number of integrations and the production of cells lines by the claimed conditions. Applicants have established this through the factual declration of Dr. Gregory Bleck. His Declaration explains why the currently claimed invention was not predictable based on the prior art as a whole and why those of skill in the art would be discouraged from attempting to approach described and claimed in the instant application..

A *prima facie* case of obviousness requires the Examiner to cite a combination of references which (a) disclose the elements of the claimed invention, (b) suggests or motivates one of skill in the art to combine those elements to yield the claimed combination, and (c) provides a reasonable expectation of success should the claimed combination be carried out. Failure to establish any one of the these three requirements precludes a finding of a *prima facie* case of obviousness, and, without more, entitles Applicant to allowance of the claims in issue.[1] In addressing this rejection, Applicants focus on the independent claims since non-obviousness of an independent claim necessarily leads to non-obviousness of claims dependent therefrom.[2]

First, the Examiner has previously admitted that Mathor does not teach the claimed limitation of 20 to 100 integrations. The other cited references do not cure this defect. Neither Coffin nor Inaba teach cells containing from 20 to 100 integrants. The references do not suggest this limitation either. In fact, the Examiner can point to no explicit or implicit statements in the references that suggest cells containing from 20-100 integrants. Even though the Examiner argues that it would be obvious to use different MOIs to achieve the claimed ranges, there is no suggestion in the references to make cells with the claimed ranges. That is what is required. As a prima facie case of obviousness has not been established because the references do not teach or suggest all of the claim limitations.

Second, Applicants respectfully submit that a person of skill in the art would not combine or modify the references to provide the claimed integration ranges. The full field of the invention must be considered. The prior art teaches away for the claimed invention as discussed above.

Applicants respectfully submit that this ground of rejection should be withdrawn.

5. The claims are not obvious over Mathor, Felts, Inaba and Burns.

Claims 1-10, 12, 14-18, 20-28 and 30-41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor in views of Felts and Inaba et al., in further view of Burns et al. This combination of references (i.e., the addition of Burns et al.) does not cure the deficiencies noted

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1 *See, e.g., Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990).

2 §MPEP 2143.03.

for the combination of Mathor, Felts, and Inaba. Burns et al., alone or in combination with the other three cited references, does not teach or suggest the claimed range of 20-100 integrants as explained in Section 4 above. Applicants respectfully request that this ground of rejection be withdrawn because the Examiner has not established a prima facie case of obviousness.

6. The claims are not obvious over Mathor, Felts, Inaba and Schroder

Claims 1-10, 12, 14-18, 20-28 and 30-41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor in views of Felts and Inaba et al., in further view of Schroder et al. This combination of references (i.e., the addition of Schroder et al.) does not cure the deficiencies noted for the combination of Mathor, Felts, and Inaba. Schroder et al., alone or in combination with the other three cited references, does not teach or suggest the claimed range of 20-100 integrants as explained in Section 4 above. Applicants respectfully request that this ground of rejection be withdrawn because the Examiner has not established a prima facie case of obviousness.

7. The claims are not obvious over Mathor, Felts, Inaba, Primus and Kolb

Claims 1-10, 12, 14-18, 20-28 and 30-41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor in views of Felts and Inaba et al., in further view of Primus and Kolb et al.. This combination of references (i.e., the addition of Primus and Kolb et al.) does not cure the deficiencies noted for the combination of Mathor, Felts, and Inaba. Niether Primus nor Kolb, alone or in combination with the other three cited references, teach or suggest the claimed range of 20-100 integrants as explained in Section 4 above. Applicants respectfully request that this ground of rejection be withdrawn because the Examiner has not established a prima facie case of obviousness.

8. The claims are not obvious over Mathor, Felts, Inaba and Naldini

Claims 1-10, 12, 14-18, 20-28 and 30-41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor in views of Felts and Inaba et al., in further view of Naldini et al. This combination of references (i.e., the addition of Naldini et al.) does not cure the deficiencies noted for the combination of Mathor, Felts, and Inaba. Naldini et al., alone or in combination

with the other three cited references, does not teach or suggest the claimed range of 20-100 integrants as explained in Section 5 above. Applicants respectfully request that this ground of rejection be withdrawn because the Examiner has not established a prima facie case of obviousness.

CONCLUSION

All grounds of rejection and objection of the Office Action of May 1, 2007 having been addressed, reconsideration of the application is respectfully requested. It is respectfully submitted that the invention as claimed fully meets all requirements and that the claims are worthy of allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicant encourages the Examiner to call the undersigned collect at (608) 218-6900.

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